REMARKS

Claims 7-16, 19 and 20 have been canceled as being drawn to non-elected invention without prejudice for filing a division application directed to this subject matter.

The Examiner has rejected claims 1-6 and 17-18 under 35 U.S.C. §112, first paragraph for lack of enablement with respect to the full scope of the claims. The Examiner contends that the specification is enabling only for *in vitro* methods for (1) inhibiting oxidative burst in neutrophils by administering hydroxymatairesinol, (2) inhibiting myeloperoxidase activity in macrophages by administering hydroxymatairesinol and (3) inhibiting Fas induced apoptosis in T-lymphocytes by administering hydroxymatairesinol, matairesinol or enterolactone. The Examiner further contends that the specification does not reasonably provide enablement for "*any* method as set forth in claims 1-6 and 17-18 for treating *any* disease such as ischemia reperfusion injury wherein the injury is myocardial infraction, stroke, transplantation, adult respiratory distress syndrome, ischemic heart disease, enterotoxic or hemorrhagic shock, or any chronic condition such as rheumatoid arthritis, any allergic condition including asthma, any inflammatory condition such as inflammatory bowel disease or skin, HIV, AIDS, psoriasis, Parkinson's disease, Alzheimer's disease, any autoimmune disease such as type I or type II diabetes, hypercholesterolemic arteriosclerosis, cataract or amylotrophic lateral sclerosis." It is submitted that the Examiner is in error in this rejection.

The present claims are directed to a method for inhibiting the overactivity of phagocytes or lymphocytes in an individual by administering an effective amount of a lignan of the specified formula. The phagocytes are specified as either (i) neutrophils or (ii) cells of myeloid origin and the lymphocytes are specified as T-lymphocytes. When the phagocytes are neutrophils, the lignan is specified as hydroxymatairesinol or matairesinol or a mixture thereof. When the phagocytes are cells of myeloid origin, the lignan is specified as enterolactone or hydroxymatairesionol or a mixture thereof. When the lymphocytes are T-lymphocytes, the lignan is specified as hydroxymatairesinol, matairesinol or enterolactone or a mixture thereof. The present claims are **not** directed to the treatment of any diseases. In fact, the Examiner restricted the present claims, i.e., claims 1-6, 17 and

18 from the claims for treating diseases, i.e., claims 7-16, 19 and 20. In view of this restriction, claims 7-16, 19 and 20 have been canceled.

Applicants submit that the Examiner's rejection is in error for the following reasons.

First, the present invention is **not** directed to the treatment of any diseases as a result of the Examiner's restriction requirement. The Examiner has concluded that the present claims for inhibiting overactivity of phagocytes or lymphocytes are patentably distinct from claims for treating diseases, such as those listed by the Examiner. Since the present claims (a) are patentably distinct from the disease treatment claims and (b) are limited to inhibiting overactivity of phagocytes or lymphocytes, the Examiner's contention concerning the lack of enablement for the treatment of any disease is not relevant to the enablement of the invention as claimed. For this reason alone, the Examiner's rejection must fail.

Second, the specification demonstrates the *in vitro* activity of the claimed lignans for the claimed cell types. Whether the activity of the claimed lignans is as good as compounds known to have similar activity is of no moment in determining enablement. The fact that the claimed lignans have activity is sufficient to show enablement. In addition, the fact that the activity of the claimed lignans has been compared with known compounds provides a basis for determining a dosage to be administered, a dosage readily determined by a skilled physician.

Third, Applicants have established that a skilled artisan has a reasonable expectation of success between *in vitro* and *in vivo* effects in a model system looking at antioxidative effects. Specifically, Applicants submit that there is a good predictability of *in vivo* effects of a drug once corresponding effects have been shown *in vitro*, as demonstrated by Dandona et al., *Circulation* **101**:122-124 (2000) and Devaraj et al., *J. Clin. Invest.* **98**:756-763 (1996) discussed in the previous Amendment.

Specifically, Dandona et al., *Circulation* **101**:122-124 (2000), demonstrates that the drug carvedilol has antioxidative effects in humans *in vivo*. In the introduction, first paragraph, Dandona states that the same drug (Carvedilol) has been shown to possess antioxidative properties, namely

scavenging peroxy and hypochlorous radicals in chemical systems *in vitro* (the *in vivo* study is shown in Aruoma, O.I., *Gen Pharmacol.* **28**:269-272 (1997), reference number 3 in the listing at the end of the text). Devaraj et al., *J. Clin. Invest.* **98**:756-763 (1996), demonstrates that alpha tocopherol (Vitamin E) has antioxidative properties in humans *in vivo*. The agent decreases the release of reactive oxygen species, lipid oxidation, interleukin-1-beta secretion and monocyte adhesion to endothelium. This agent had earlier been shown to possess antioxidative properties *in vitro* (see Burton et al. *Ann. NY Acad. Sci.* **570**:7-22 (1989), reference number 55 in the listing at the end of the text).

Both of these two references show that, contrary to the Examiner's contention, there is a clear correlation between test results *in vitro* and effects for the tested drugs *in vivo*. The Examiner contends that these references do not support Applicants' position because they do not describe lignans. The fact that these references do not describe lignans is not relevant to the question of predictability with respect to *in vitro* and *in vivo* activity. These references clearly demonstrate that a skilled artisan would predict with a reasonable expectation of success that compounds which are active in the *in vitro* model are active *in vivo*. Thus, a skilled artisan would predict with a reasonable expectation of success that the claimed lignans having the *in vitro* activity demonstrated in the present application for the claimed cell types would have *in vivo* activity with respect to these same cell types.

The specification clearly demonstrates that the claimed lignans have the claimed activity, i.e., inhibition of overactivity of the claimed cell types. Specifically, Applicants submit that Table 1 shows both hydroxymatairesinol and matairesinol (i.e., all of the lignans claimed for this aspect) have effect on neutrophils, as shown by oxidative burst and myeloperoxidase activity. Nitecapone and 4-OH-toremifene are both very strong antioxidants. The fact that matairesinol requires a higher dose than the very strong reference compounds for oxidative burst does not mean that matairesinol in ineffective. For myeloperoxidase activity, is should be noted that both hydroxymatairesinol and matairesinol fall between the results of the two strong reference compounds. Therefore, it is shown

that both hydroxymatairesinol and matairesinol have an effect on neutrophils, measured by oxidative burst and myeloperoxidase activity. Applicants believe it to be unjust if, in order to claim a new use of a compound, they were made to show that the compound shows a stronger property than the strongest known compound for said use.

Example 2 and Figures 2 and 3 show that hydroxymatairesinol, matairesinol and enterolactone all have an effect on T-lymphocytes. Thus, the claimed aspect is fully supported. Example 3 and the Figures 4 show that enterolactone and matairesinol have effects on cells of myeloid origin, in that they decrease TNF-alpha production. It is evident to a skilled artisan that mixtures are also useful once the individual compounds have been shown to work.

The Examiner appears to believe that Table 1 relates to the effect on phagocytes of myeloid origin. This is an erroneous assumption. Table 1 shows the effects on neutrophils. Effects on cells of myeloid origin are shown in Example 3 and in the Figures 4.

Thus, this data in combination with the known correlation between *in vitro* and *in vivo* activity would lead a skilled artisan to predict that the claimed lignans have the claimed activity *in vivo* with a reasonable expectation of success.

Fourth, the Examiner contends that the Pool-Zobel et al. teaches that a lignan such as enterolactone reduces oxidized bases at high, non-physiological concentrations but has no effect on oxidative stress. Applicants submit that Pool-Zobel et al. does not contain any information on the basis of which such a conclusion could be drawn. **Both of the Figures 4 and 5 of Pool-Zobel et al. relates to *in vitro* experiments.** Pool-Zobel et al. does not disclose any *in vivo* experiment. The statement in the article saying that "enterolactone reduces oxidized bases at high, non-physiological concentrations" refers obviously to the *in vitro* experiments disclosed in Figure 4. The continuing wording in the sentence "but had no effect on oxidative stress" refers to the *in vitro* experiment disclosed in Figure 5. Furthermore, Applicants submit that **the cells used in the Pool-Zobel et al. experiments are entirely different from the phagocytes and lymphocytes which are affected according to the present invention**. Applicants submit that the fact that the *in vitro* experiment

showed no effect on oxidative stress in cells of a different cell type than those claimed cannot be used as grounds for a conclusion that no *in vivo* effect would be obtained on the claimed cells, in view of the *in vitro* data set forth in the application and the reasonable expectation of success by a skilled artisan in view of the model systems as described above.

Fifth, the Examiner contends that the method for inhibiting overactivity of phagocytes or lymphocytes in an individual is unpredictable in the absence of *in vivo* data. He has asserted that the lignan may be inactivated before producing an effect, such as by proteolytic degradation, immunological inactivation or due to an inherently short half-life of the lignan. Applicants point out that the claimed lignans are not proteins. Consequently, none of these assertions are valid for the present invention. In this context, Applicants note that the case cited by the Examiner (*Ex parte Aggarwal*, 23 USPQ2d 1334 (BPAI 1992) is not on point. Specifically, the invention in *Aggarwal* was directed to the treatment of tumors, which the Board noted was unpredictable, using a protein. The presently claimed invention does not relate to the treatment of tumors and does not involve the use of a protein, i.e., lignans are not proteins. Accordingly, *Aggarwal* is not precedent with respect to the presently claimed invention.

In addition, it is submitted that it is the function of the FDA and not the Patent Office to determine the efficacy of drugs and to approve them for use. Thus, the mere supposition of efficacy issues by the Examiner, unsupported in the record, is not basis for a rejection for lack of enablement. In fact, Applicants note that the Examiner has cited art, i.e., the Pool-Zoble et al. reference, which does not show any side effects for lignans. This reference further demonstrates that there is no basis for the Examiner's suppositions concerning the *in vivo* activity of the lignans presently claimed.

Sixth, the Examiner relies on *The Merck Manual* to assert that it does not recognize the use of any lignan for inhibiting overactivity of phagocytes or lymphocytes, and thus a skilled artisan could not predict activity of the claimed lignans. The fact that *The Merck Manual* does not show use of the claimed lignans for inhibiting overactivity of phagocytes or lymphocytes is not surprising, since it is this activity of the claimed lignans which is the invention of the present application. If

such use was described in *The Merck Manual*, then it would be anticipated. The mere fact that the use is not described in *The Merck Manual* is not in itself evidence of unpredictability. The unpredictability must be determined on the basis of the disclosure in the present application in view of the skill in the art and the knowledge of the skilled artisan and not on the basis of *The Merck Manual* alone.

Seventh, the "examiner has the initial burden to establish a reasonable basis to question the enablement provided for the **claimed** invention." MPEP2164.04, *citing In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir.1993) (emphasis added). In *Wright*, the Court made clear that the PTO has the burden of providing a reasonable explanation of why the specification does not enable. Furthermore, there must be some reason to doubt the objective truth of the statements in the specification. M.P.E.P. § 2164.04; *In re Marzocchi*, 169 USPQ 367 (CCPA 1973). Applicants submit that the Examiner has not provided acceptable evidence to doubt the objective enablement of the specification and to support his contention that the specification is not enabling. As the Court said in *Marzocchi*,

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis [i.e. doubt of the objective truth of statements in the specification] is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go through the trouble and expense for supporting his presumptively accurate disclosure.

169 U.S.P.Q. at 370. In the absence of suitable evidence, the Examiner has not met his burden of establishing non-enablement.

As demonstrated above, the Examiner's statements concerning administration of the claimed lignans and reliance on *Aggarwal* are factually flawed and incorrect and are not evidence which can serve to rebut the objective truth of the statements made in the specification. Similarly, the Examiner's reliance on *The Merck Manual* is flawed and incorrect and is not evidence which can serve to rebut the objective truth of the statements made in the specification. In addition, the

Examiner's comments concerning the treatment of disesases which are not the subject matter of the present claims is not evidence which can serve to rebut the objective truth of the statements made in the specification. Finally, the Examiner's dismissal of the evidence Applicants have provided to show a reasonable expectation of success between *in vitro* and *in vivo* activity is based on flawed and incorrect analysis of the teachings of these references. Consequently, the Examiner has failed to provide acceptable evidence which would cast doubt on the objective enablement of the specification.

Since the Examiner has not presented any acceptable scientific evidence or reasons to doubt the objective enablement of the specification for the method for inhibiting the overactivity of the specified phagocytes or lymphocytes by the administration of hydroxymatairesinol, matairesinol and enterolactone, a proper case for lack of compliance with the enablement provision of 35 U.S.C. §112, first paragraph has not been established. Furthermore, the references cited by Applicants have established that the area is not unpredictable, especially with respect to *in vitro* and *in vivo* activity, and therefore support the objective enablement of the specification. These references demonstrate the reasonable expectation of success in the art for the claimed invention. Applicants have provided examples in the specification of the claimed activity of the claimed lignans with respect to the claimed cell types. Applicants have provided guidance in the specification as to which lignans to use with which cell types. The claims are narrow, being directed only to the inhibition of overactivity of certain claimed cell types by certain claimed lignans. The issue for a Section 112 rejection is not whether any experimentation would be required, but whether such experimentation would be undue. All of the facts detailed above clearly establish that a skilled artisan can practice the claimed invention without an undue amount of experimentation, and thus the claimed invention is enabled.

In view of the above remarks, it is submitted that claims 1-6 and 17-18 are fully enabled by the specification. Withdrawal of this rejection is requested.

In view of the above amendments and remarks, it is submitted that the present claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration and early notice of allowance are requested. The Examiner is invited to telephone the undersigned in order to expedite prosecution of the present application.

Respectfully submitted,

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